Adjudication of cardiovascular events in patients with chronic obstructive pulmonary disease: SUMMIT trial

Original Article

Adjudication of cardiovascular events in patients with chronic obstructive pulmonary disease: SUMMIT trial

Robert A Wise[1,*], Julie A Anderson[2], Pierre Amarenco[3], Nicholas J Cowans[4], Courtney Crim[5], Martin A Denvir[6], Camilo R Gomez[7], Matthew PA Jones[4], Andrea Morris[5], Dennis Niewoehner[8], Julie C Yates[5]

Running title: Cardiovascular events from the SUMMIT trial

Word count: 3,199~~64~~

Affiliations

[1]Division of Pulmonary and Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA

[2]Research & Development, GSK, Stockley Park, Middlesex, UK

[3]Department of Neurology and Stroke Centre, Paris-Diderot-Sorbonne University, Paris, France

[4]Statistics and Programming, Veramed Ltd., Twickenham, UK

[5]Research & Development, GSK, Research Triangle Park, NC, USA

[6]Centre for Cardiovascular Science, University of Edinburgh, Edinburgh, UK

[7]Department of Neurology, Loyola University Chicago, Stritch School of Medicine, Maywood, IL, USA

[8]Pulmonary, Critical Care and Sleep Apnea, Minneapolis Veterans Affairs Health Care System, and University of Minnesota, Minneapolis, MN, USA

***Corresponding author:** Pulmonary and Critical Care, Johns Hopkins University School of Medicine, 5501 Hopkins Bayview Circle, Baltimore, MD 21224, USA.

Email: rwise@jhmi.edu

Phone: 410 550-0546

Funding support: This work was supported by GlaxoSmithKline plc. (HZC113782).

Clinical trial registration: NCT01313676

Abstract

Background: Adjudicated cause-specific mortality has been used in major trials of chronic obstructive pulmonary disease (COPD). However, there is less experience with adjudicated major adverse cardiovascular events (MACE) as a key efficacy outcome in COPD trials. The Study to Understand Mortality and Morbidity in COPD (SUMMIT) ~~study~~ trial required a Clinical Endpoint Committee (CEC) to adjudicate the outcomes of modified MACE and cause-specific mortality.

Methods and results: A six-member CEC reviewed adverse event ~~(AE)~~ and serious adverse event ~~AE (SAE)~~ reports included in a list of 204 Medical Dictionary for Regulatory Activities ~~MedDRA~~ terms. Adverse events ~~AEs~~ were triaged by one CEC member then reviewed by three reviewers (round 1). If these three disagreed on the adjudication, the event was discussed by the full committee to reach a consensus (round 2). Among 16,485 participants, 48,105 adverse events ~~AEs~~ were reported, among which 3314 were reviewed by the CEC. After triage, 1827 were adjudicated in round 1; 338 required committee consensus in round 2, yielding 450 myocardial infarctions, strokes, unstable anginas or transient ischaemic attacks. Only 20/1627 (1%) non-serious adverse events ~~AEs~~ were adjudicated as cardiovascular events. Only 45/204 Medical Dictionary for Regulatory Activities ~~MedDRA~~ terms reviewed yielded cardiovascular events. 430 deaths were adjudicated in round 1 and 631 in round 2, yielding 459 cardiovascular deaths. Adjudication of chest pain and sudden death often required additional information from site investigators. Site assessment of cardiovascular death was moderately specific (501/602=83%) but not sensitive (256/459=56%).

Conclusions: A CEC is useful for adjudication of MACE in COPD trials but requires considerable resources and effort by investigators. This process can be streamlined by reviewing only ~~SAEs~~ serious adverse events and filtering by selected Medical Dictionary for Regulatory Activities ~~MedDRA~~ terms.

Clinical trial registration: NCT01313676 https://clinicaltrials.gov/ct2/show/NCT01313676

Keywords: COPD mortality, MACE adjudication, myocardial infarction, stroke, unstable angina

Abbreviations: ~~AE, adverse event;~~ CEC, Clinical Endpoint Committee; COPD, chronic obstructive pulmonary disease; ~~ECG, electrocardiograph; FDA, Food and Drug Administration; FEV_1, forced expiratory volume in 1 second; FF/VI, furoate/vilanterol;~~ MACE, major adverse cardiovascular events; SUMMIT, Study to Understand Mortality and Morbidity in COPD~~MedDRA, Medical Dictionary for Regulatory Activities; MI, myocardial infarction; SAE, serious adverse event; TIA, transient ischaemic attack; UA, unstable angina; VCAS, Virtual Clinical Adjudication System~~.

Introduction

Cardiovascular co-morbidities are common in chronic obstructive pulmonary disease (COPD) and often lead to major adverse cardiovascular events (MACE). Cause-specific mortality has become a routine adjudicated outcome in large COPD clinical trials, and the methods and experience of the adjudication process have been reported previously.[1–3] Although MACE is a common outcome measure in cardiovascular clinical trials, it has not been widely used as an adjudicated efficacy or safety outcome for COPD trials. The Study to Understand Mortality and Morbidity in COPD (SUMMIT) was a large COPD clinical trial that tested the secondary hypothesis that fluticasone furoate/vilanterol ~~(FF/VI)~~ combination treatment would reduce risk of MACE in mild-moderate COPD patients with increased cardiovascular risk factors.[4,5] To this end, SUMMIT required the development of a process and procedures for collecting and adjudicating cause-specific mortality and MACE. For SUMMIT, the definition of MACE included transient ischaemic attacks ~~(TIA)~~ and unstable angina ~~(UA)~~ as well as myocardial infarction ~~(MI)~~, stroke, and cardiovascular death. To accomplish this task, a Clinical Endpoint Committee (CEC) was established and principles of operation, based on published guidelines for cardiovascular trials, were adapted for review of SUMMIT events. From the extensive experience accrued from this study, we learned lessons that may be employed in future COPD trials in which MACE is an efficacy or a safety outcome. The purpose of this report is to provide post hoc details of the process, the efficiency of MACE ascertainment methods, and the extent of agreement between adjudicated events and site-investigator reports, and to provide recommendations for future adjudication committees.

Methods

SUMMIT study design

The SUMMIT study design and primary outcomes have been previously reported.[4,5] Briefly, the trial was a randomised, double blind, parallel group event-driven trial comparing fluticasone furoate/vilanterol ~~FF/VI~~ and placebo, inhaled once daily. Enrolled participants had moderate COPD (post-bronchodilator forced expiratory volume in 1 second ~~[FEV$_1$]~~ 50–70% predicted) and increased risk for cardiovascular disease. Each participant was followed from enrolment to at least the common end date, at which there were projected to be 1000 deaths. The primary outcome was all-cause mortality up to the common end date, however all deaths reported before the database was locked were adjudicated. The secondary outcomes were rate of decline in forced expiratory volume in 1 second ~~FEV$_1$~~ and a cardiovascular composite endpoint (MACE) comprising on-treatment ~~MI~~myocardial infarction, stroke, transient ischaemic attack~~TIA~~, unstable angina~~UA~~ and cardiovascular death. All patients provided written informed consent. The study was approved by local ethics committees and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Acquisition of medical information

When a participant died or reported any adverse event ~~(AE)~~ to the local site, the adjudication process was initiated. For each death, the site was asked to provide as much information as possible to facilitate the adjudication of the primary cause of death including death certificate, hospital correspondence,

results of clinical investigations, procedure reports, witness interviews and autopsy results where available. When a site reported an adverse event ~~AE~~ into the electronic case report form, the verbatim term was coded by a central automatic coding procedure to a ~~MedDRA (~~Medical Dictionary for Regulatory Activities (~~,~~version 18) preferred term. If this Medical Dictionary for Regulatory Activities ~~MedDRA~~ term matched~~mapped to~~ a list of preferred terms of pre-defined events, then the adverse event ~~AE~~ was sent for adjudication for a ~~CV~~cardiovascular event. ~~from MedDRA (Medical Dictionary for Regulatory Activities, version 18)~~. These pre-defined events were chosen by a physician reviewing all Medical Dictionary for Regulatory Activities ~~MedDRA~~ preferred terms prior to the adjudication process starting. For these events, sites were also requested to provide all available medical records to support the determination of causation of death and hence whether this was a component of MACE.

Commented [JL1]: *Amended to address Reviewer 2, comment 2.*

Operation of the Clinical Endpoint Committee

The CEC comprised six physicians, two each from the following specialties: Pulmonology, Cardiology and Neurology. The CEC members were not site investigators in the study. The committee members were selected by the sponsor and approved by the SUMMIT steering committee. The CEC operated under a charter written by the sponsor and created a principles of operation document that was written by the CEC members and was updated throughout the study to codify guidelines for adjudicating the cardiovascular events (see Online Supplementary Appendix A).

Data management

The ~~Virtual~~ virtual ~~Clinical~~ clinical ~~Adjudication~~ adjudication ~~System~~ system ~~(VCAS)~~ was a web-based application for central management of information retrieval and adjudication activities developed for

SUMMIT (PAREXEL, Waltham, MA, USA). When an event occurred for a subject, relevant clinical documents were collected in the virtual clinical adjudication system ~~VCAS~~ to create an electronic dossier. Reviewers recorded their assessments in the virtual clinical adjudication system ~~VCAS~~ and if discordance was found, the case was automatically distributed for consensus review.

Adjudication of cause-specific death and MACE

The process for adjudicating the primary cause of death and assessing whether or not it was related to COPD was similar to that followed in recent large respiratory trials.[1–3] In brief, the adjudicated cause of death was classified based on the underlying cause of death defined as the presenting illness that preceded the terminal events, not the terminal events just preceding death. Adjudication of MACE events generally followed the Food and Drug Administration ~~(FDA)~~ guidance for cardiovascular outcomes.[6]

Sudden death is a term generally denoting a presumed arrhythmic death when the death is witnessed (i.e. the person is found dead ~~seen alive~~ within 1 hour of being ~~-~~seen alive~~found dead~~), and another cause could not be identified. In SUMMIT it was included as a subcategory of cardiovascular deaths. If a death was unwitnessed and occurred within 1–24 hours of the patient last being seen alive without evidence of clinical deterioration and no other cause of death was ascertained, it was also categorised as a sudden death as well as a cardiovascular death. If the interval between death and last being observed alive was greater than 24 hours, and there was no other cause of death, the death was classified as unknown. This information was systematically obtained by the sites for deaths occurring outside of medical facilities by a standardised interview with a family member or witness.

Commented [JL2]: *Authors, please advise if this edit is incorrect*

Myocardial ~~Infarctions~~ infarctions were adjudicated using published criteria using cardiac enzymes, electrocardiograph ~~(ECG)~~ changes, imaging or pathologic evidence.[7] Stroke was diagnosed based on compatible neurologic symptoms supported by brain imaging or onset of a typical acute neurologic deficit. Unstable angina was diagnosed based on the need for unscheduled medical care associated with compatible electrocardiograph ~~ECG~~ or imaging evidence of coronary stenosis or need for a revascularisation procedure. Transient ischaemic attack was defined as a witnessed, transient compatible neurologic deficit lasting less than 24 hours in the absence of imaging evidence of a stroke. Amaurosis fugax, although representing ocular rather than brain ischaemia, was also classified as a ~~TIA~~transient ischaemic attack.

Adjudication procedures

Potential MACE events were adjudicated in three stages: a triage round by one committee member, round 1 adjudication by three committee members, and round 2 by the entire committee of six. All non-serious ~~AEs~~ adverse events that matched the selected list of Medical Dictionary for Regulatory Activities ~~MedDRA~~ preferred terms was assigned to a single member of the committee in the triage round. The committee member reviewed the available documentation and determined whether the event warranted further adjudication. If yes, the event was escalated to round 1. All deaths and serious adverse events~~AEs (SAEs)~~ were automatically assigned to round 1. In round 1, each event and all the accompanying information was sent to three CEC members, one of each specialty. If all three members adjudicated the event in an identical fashion, the event was considered adjudicated. If there was disagreement on any field of the adjudication form, then the event was escalated to round 2, which was a face to face meeting or internet conference with all six members discussing the event and associated source material to reach consensus.

Results

Overall, among the 16,485 participants, SUMMIT reported 48,105 on-treatment adverse events ~~AEs~~ (includes fatal and non-fatal), of which 3,314 (7%) matched the list of pre-defined MedDRA preferred terms. These were subsequently reviewed by the CEC. Of these, 1,687 were ~~SAEs~~ serious adverse events and 1,627 were non-serious adverse events~~AEs~~. 450 ~~AEs~~ adverse events were adjudicated as ~~MI~~myocardial infarctions, strokes, ~~TIA~~ transient ischaemic attacks or ~~UA~~unstable angina, of which 387 were non-fatal. Only 20 (1%) of the 1,627 non-serious adverse events ~~AEs~~ were finally adjudicated as cardiovascular events, whereas 430 (25%) of the 1,687 serious adverse events ~~SAEs~~ were finally adjudicated as cardiovascular events. Of these 450 adjudicated events 43% were myocardial infarctions~~MI~~, 30% were strokes, 19% were unstable angina~~UA~~, and 8% were transient ischaemic attacks ~~TIA~~ (Figure 1a). Out of 70 transient ischaemic attacks ~~TIA~~ preferred terms, 30 (43%) were adjudicated as cardiovascular events.

Of the 1,061 deaths in the study, 1,037 (98%) were in the intent-to-treat population and occurred on or before the common end date so were included in the SUMMIT primary analysis.[5] Of the 1,061 total deaths, 4% were ~~an~~ myocardial infarctions~~MI~~, 4% were strokes, 30% were sudden deaths, 1% were procedural deaths, and 5% were of other cardiovascular causes (e.g. aortic aneurysm), giving a total of 459 (43%) classified as cardiovascular death. The other causes of death included cancer (23%), pulmonary (13%), other causes (8%), and unknown cause (12%) (Figure 1b).

Because the secondary outcome measure of interest was time to first event, participants who had two events had only the first event included in the primary analysis, consisting of 688 first on-treatment cardiovascular events (359 non-fatal and 329 fatal, ~~Figure 1c~~Table 2).

To capture all events that could be potentially a MACE, the committee reviewed events described by 204 Medical Dictionary for Regulatory Activities ~~MedDRA~~ terms that occurred in the study. However, only 45 of the 204 Medical Dictionary for Regulatory Activities ~~MedDRA~~ terms that were used to filter events for adjudication finally yielded an adjudicated MACE~~.~~ (Online Supplementary Appendix B, Figure S1 and Table S1). Some terms were very specific. For example, 82/97 (85%) events with the preferred term 'acute myocardial infarction' and 73/115 (63%) with the preferred term 'myocardial infarction' were adjudicated as MACE. In contrast, only 8/352 (2%) of events with the term 'chest pain' were finally adjudicated as a MACE.

Agreement among adjudicators

In general, the CEC had good agreement and was able to adjudicate 317 (70%) of the non-fatal MACE with all three adjudicators agreeing on all elements of the adjudication in round 1. Of the 450 non-fatal MACE, 133 (30%) required promotion to the full six-member committee where a consensus was reached in all cases.

Overall, there was good agreement between individual adjudicators and the final committee consensus with respect to the primary class of death (e.g. cardiovascular, pulmonary, cancer). Among the six adjudicators a total of 3,878 records were reviewed initially and 3,286 (85%) were ultimately consistent with the committee's final adjudication. The percent agreement of individual adjudicators ~~agreement~~ with the final cause of death category ranged from 75% to 91% (~~online~~ Online Supplementary Appendix B, Table S2).

Agreement with site investigators

As noted in prior COPD trials, the agreement between the CEC and the site investigator for underlying cause of death varied by category. In general, there was good agreement for cancer related deaths, the CEC agreeing with the investigator in 192/194 (99%) of cases whereas the committee agreed with the site investigator in only 256/357 (72%) of cases initially classified by the site investigator as a cardiovascular death (Table 1).

Overall, the site investigator classifications had a specificity of 83% (501/602) and a sensitivity of 56% (256/459) with regards to cardiovascular deaths.

Commented [JL3]: *Added to address Reviewer 2, comment 10.*

Discussion

In this manuscript, we present the operations and outcomes of the SUMMIT CEC to adjudicate MACE in patients with mild-moderate COPD and at risk for cardiac disease. ~~Although cause-specific mortality has been well-established as an outcome measure for large-scale clinical trials in COPD,~~ SUMMIT was the first major COPD clinical trial to incorporate MACE as a key efficacy outcome measure, rather than ~~. In general, when MACE is reported in COPD trials, it is used as a safety measure~~evaluating this in the context of safety.[8] Because cardiovascular events are common in patients with COPD, and ~~because~~ these events are often preceded by COPD exacerbations, it seems likely that future treatment trials targeting COPD exacerbations will place greater scrutiny on these as key clinical outcomes.~~,~~[8,9] ~~Procedures for adjudication of MACE and cardiac death have been widely used in heart disease trials, but that experience has been less frequently reported for COPD outcomes and has been evaluated in the context of safety rather than efficacy.[9] We~~ thus we report here our experience ~~with a large trial of mild-moderate COPD patients at risk for cardiac disease~~ in order to report lessons learned and provide recommendations for future studies.

In organising the CEC for a trial the size of SUMMIT, it was necessary to construct a large infrastructure to collect, organise, translate, and distribute the pertinent case report forms and clinical source material and documents that were reviewed by the committee, and to triage reports using a staged approach. ~~In SUMMIT, this was facilitated by the development of a data platform (VCAS) that allowed CEC members to review collected information and to complete adjudication forms electronically. Because of the scope of the review, it was not possible to have all six committee members review all cases, so we used a staged approach that permitted triage of reports. First, all AEs were filtered by specific terms that~~

Commented [JL4]: *Authors, we have added some proposed amendments to this paragraph as noted in the response to reviewers file (reviewer 2, comment 8) – no changes had been tracked here in the file you kindly provided so please do advise if changes had already been made and should be tracked from the originally submitted version.*

~~suggested possible MACE. Second, non-serious AEs of interest were triaged by a committee member to exclude unlikely events. Third, SAEs and non-serious AEs that were not excluded by triage were reviewed by three committee members. If the three committee members did not agree entirely, the event was promoted to the full review by the six-member committee for development of a consensus.~~ Ultimately, the committee was able to reach a consensus in every case, although sometimes this required tabling an event for review at a second meeting. The initial in-person meetings, and discussion of example cases to establish rules for evaluation of cases, along with written principles of operation to codify these criteria was helpful for establishing the norms for the committee. It was also helpful to have specialised expertise in neurology, cardiology, pulmonary and critical care for evaluation of difficult cases.

Commented [JL5]: *Authors, we have added some proposed amendments to this paragraph as noted in the response to reviewers file (reviewer 2, comment 9) – no changes had been tracked here in the file you kindly provided so please do advise if changes had already been made and should be tracked from the originally submitted version.*

We learned from this experience that the effort involved in reviewing non-serious reports of events yielded few MACE events, even after filtering for cardiovascular and related terms, with only 1.2% of these reviews ultimately yielding an outcome event, accounting for only 4% of the final total MACE. Therefore, in circumstances where resources are particularly constrained, it may be justified to review only ~~SAEs~~serious adverse events, i.e. those that lead to hospitalisation, death or are considered life-threatening.

Even among ~~SAEs~~ serious adverse events where medical records were available, some diagnostic terms were challenging for the committee. For example, the diagnosis of ~~UA~~ unstable angina presented a challenge to the committee requiring a second round of review in 39% of cases. We found that the hospital diagnosis of unstable angina ~~UA~~ was often used for patients with stable angina who were admitted to the hospital for elective procedures such as coronary arteriography. In line with the ~~FDA~~ Food and Drug Administration draft guidance, the committee required three elements to adjudicate

unstable anginaUA: 1) a pattern of symptoms compatible with unstable anginaUA, 2) an urgent, unscheduled admission to a healthcare facility, and 3) anatomic evidence of coronary artery disease or performance of a coronary intervention. With this definition, of 88 events with an SAE severe adverse event coded as unstable anginaUA, 6 (7%) were adjudicated as a myocardial infarctionn MI, and only 32 (36%) were adjudicated as unstable anginaUA. Thus, a revascularisation procedure per se did not constitute a MACE event unless it was in the context of an acute worsening of symptoms.

TIAs Transient ischemic attacks were also challenging to adjudicate because of the requirement for definite evidence of neurologic symptoms and absence of findings of stroke. Among 45 severe adverse events SAEs that were reported as transient ischemic attacksTIAs, only 24 (53%) were finally adjudicated as transient ischemic attacksTIA. We also note that congestive heart failure events were reported only 187 times and that only 2.7% were adjudicated as MACE. We speculate that this low yield may be due to the difficulty in distinguishing acute left ventricular failure from an exacerbation of COPD with cor pulmonale, emphasizing the need for consistent adjudication of both cardiovascular events and COPD exacerbations.

Commented [JL6]: *Added to address Reviewer 1, comment 1.*

In contrast, severe adverse events SAEs with the diagnosis of 'acute myocardial infarction' were more accurate – adjudicated as an myocardial infarctionMI 81% of the time (78/96 events). If the severe adverse event SAE Medical Dictionary for Regulatory Activities MedDRA term was simply 'myocardial infarction', then only 73/114 (64%) events adjudicated as a myocardial infarctionn MI. Based on this experience, caution is warranted in the use of severe adverse events SAEs as reliable surrogates for MACE events in clinical trials.

The committee also classified all myocardial infarctions MIs as either type 1 (coronary artery obstruction) or type 2 (oxygen-demand ischaemia). COPD exacerbations increase the risk of an

myocardial infarction ~~MI~~ about 2 to 4-fold after a COPD exacerbation.[8,10] It has been hypothesised that these events are brought on by increased myocardial oxygen demands from the combination of hypoxemia and beta-agonist use raising the hypothesis that there would be an excess of type 2 myocardial infarctions ~~MIs~~ in a COPD population. This was not found to be the case. In observational series of acute myocardial infarction~~MI~~, only 10–14% are classified as type 2 events.[11,12] This is comparable to the experience in SUMMIT where, of 173 myocardial infarctions~~MIs~~, 20 (11.5%) were adjudicated as type 2 events. Thus, it seems plausible that other factors such as increased platelet aggregation are related to the risk of myocardial infarction ~~MI~~ and stroke immediately following a COPD exacerbation.[13]

Early in the operation of the committee, we found that the ~~AE~~ adverse event of 'chest pain' or 'chest discomfort' was a frequent occurrence and that medical records were sparse. To better evaluate these reports, we provided site investigators with a specific questionnaire to assess whether this was likely due to ischaemic heart disease. Among 389 adverse events ~~AEs~~ that were not considered serious, only 3 (0.7%) were adjudicated as a MACE event (2 myocardial infarction ~~MI~~ and 1 unstable angina~~UA~~). The yield was higher from the term 'chest pain' when it was associated with a~~n~~ ~~SAE~~ serious adverse event. Among 53 such serious adverse events~~SAEs~~, 6 (11%) were adjudicated as MACE (4 myocardial infarction ~~MI~~ and 2 unstable angina~~UA~~).

Assessment of sudden or unwitnessed death is a particularly difficult problem in COPD populations since some of these deaths may be the result of respiratory events as well as cardiovascular death.[5] In line with previous adjudication committees,[1–3,14] we used arbitrary definitions of sudden death in the absence of a presenting acute illness and relied upon interviews with family or caretakers to help in this process. Among 320 deaths finally adjudicated as sudden death, only 189 (59%) were reported as such

Commented [JL7]: *References added to address Reviewer 1, comment 1 and Associate Editor, comment 2.*

by site investigators. When the death was unwitnessed, but the participant was found dead within 24 hours of being in usual health (often a nocturnal event), the committee had to review the case as a whole in round 2 in 111/156 cases (71%) which was the most frequent death event requiring full committee consensus with only 45/156 (29%) reaching agreement at round 1. When the death was witnessed within 1 hour, there was greater consensus with 82/164 (50%) of these events confirmed on round 1, and 82/164 (50%) requiring discussion of the full committee.

In summary, we report here the procedures and experience of the SUMMIT CEC with respect to cause-specific mortality and MACE. A major lesson that we have derived from this experience is that an extensive infrastructure and defined procedures are necessary to accomplish these adjudications. We also observed that only 22% of preferred Medical Dictionary for Regulatory Activities ~~MedDRA~~ terms yielded adjudicated events and that ~~AEs~~ adverse events that were not considered to be serious events rarely yielded MACE events. Thus, in future studies, considerable efficiency could be achieved by tighter filtering of terms reviewed by the committee or even eliminating review of events not deemed serious by the site investigator. Although all-cause mortality is a more robust outcome measure in clinical trials than cause-specific mortality, assessment of cardiovascular death is an important component of MACE where cardiovascular safety or efficacy outcomes are critical. In this case, we believe that it is essential to rely on an adjudication committee for this outcome rather than site investigator reports. Considering the CEC adjudication of cardiovascular deaths as the reference standard, site investigator classification was not particularly reliable with a specificity of 83% (501/602) and a sensitivity of only 56% (256/459). This contrasts with cancer-specific mortality where site investigators had a high degree of reliability.

Funding support

This work was supported by GlaxoSmithKline plc. (HZC113782).

Data accessibility

Anonymised individual participant data and study documents can be requested for further research from www.clinicalstudydatarequest.com

Acknowledgements

The authors would like to thank the SUMMIT steering committee, composed of academic experts and employees from GlaxoSmithKline plc., who were responsible for the scientific oversight of the trial, the study design and analysis, and for the review and interpretation of the data.

Competing interests

RAW, PA, MAD, CRG, DN are members of the SUMMIT CEC. JAA, CC, and JCY are members of the SUMMIT Steering Committee. JAA, CC, AM and JCY are employed by GSK. NJC and MPAJ are employees of Veramed Limited, a contract research organisation that receives funding from GlaxoSmithKline plc.

Members of the SUMMIT Steering Committee

Jorgen Vestbo (co-chair, UK), Robert D. Brook (USA), Peter M.A. Calverley (UK), Bartolome R. Celli (USA), Fernando Martinez (USA), David E. Newby (UK), Courtney Crim, (co-chair, GlaxoSmithKline plc., USA), Julie A. Anderson (GlaxoSmithKline plc., UK), Julie C. Yates (GlaxoSmithKline plc., USA).

Members of the SUMMIT Clinical Endpoint Committee

Robert A. Wise (chair, USA), Dennis Niewoehner (USA), Camilo R. Gomez (USA), Sheldon Magder (Canada), Martin A. Denvir (UK), Pierre Amarenco (France).

References

1. McGarvey LP, John M, Anderson JA, et al. Ascertainment of cause-specific mortality in COPD: operations of the TORCH Clinical Endpoint Committee. *Thorax* 2007; 62: 411–415.
2. McGarvey LP, Magder S, Burkhart D, et al. Cause-specific mortality adjudication in the UPLIFT® COPD trial: findings and recommendations. *Respir Med*. 2012; 106: 515–521.
3. Wise RA, Kowey PR, Austen G, et al. Discordance in investigator-reported and adjudicated sudden death in TIOSPIR. *ERJ Open Res*. 2017; 3: pii: 00073-2016.
4. Vestbo J, Anderson J, Brook RD, et al. The Study to Understand Mortality and Morbidity in COPD (SUMMIT) study protocol. *Eur Respir J*. 2013; 41: 1017–1022.
5. Vestbo J, Anderson JA, Brook RD, et al. Fluticasone furoate and vilanterol and survival in chronic obstructive pulmonary disease with heightened cardiovascular risk (SUMMIT): a double-blind randomised controlled trial. *Lancet* 2016; 387: 1817–1826.
6. Hicks KA, Mahaffey KW, Mehran R, et al. 2017 Cardiovascular and Stroke Endpoint Definitions for Clinical Trials. *J Am Coll Cardiol*. 2018; 71: 1021–1034.
7. Thygesen K, Alpert JS, White HD; Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction. Universal definition of myocardial infarction. *Circulation* 2007;116:2634–2653.
8. White WB, Cooke GE, Kowey PR, et al. Cardiovascular safety in patients receiving roflumilast for the treatment of COPD. *Chest* 2013; 144: 758–765. ~~Donaldson GC, Hurst JR, Smith CJ, et al. Increased risk of myocardial infarction and stroke following exacerbation of COPD. *Chest* 2010; 137: 1091–1097.~~

9. Donaldson GC, Hurst JR, Smith CJ, et al. Increased risk of myocardial infarction and stroke following exacerbation of COPD. *Chest* 2010; 137: 1091–1097. ~~White WB, Cooke GE, Kowey PR, et al. Cardiovascular safety in patients receiving roflumilast for the treatment of COPD. *Chest* 2013; 144: 758–765.~~

10. Kunisaki KM, Dransfield MT, Anderson JA, et al. Exacerbations of chronic obstructive pulmonary disease and cardiac events. A post hoc cohort analysis from the SUMMIT randomized clinical trial. *Am J Respir Crit Care Med*. 2018; 198: 51–57.

11. López-Cuenca A, Gómez-Molina M, Flores-Blanco PJ, et al. Comparison between type-2 and type-1 myocardial infarction: clinical features, treatment strategies and outcomes. *J Geriatr Cardiol.* 2016; 13: 15–22.

12. Gupta S, Vaidya SR, Arora S, et al. Type 2 versus type 1 myocardial infarction: a comparison of clinical characteristics and outcomes with a meta-analysis of observational studies. *Cardiovasc Diagn Ther*. 2017; 7: 348–358.

13. Muñoz-Esquerre M, Ferreiro JL, Huertas D, et al. Impact of acute exacerbations on platelet reactivity in chronic obstructive pulmonary disease patients. *Int J Chron Obstruct Pulmon Dis*. 2017; 13: 141–148.

14. Wise RA, Chapman KR, Scirica BM, et al. Effect of Aclidinium Bromide on Major Cardiovascular Events and Exacerbations in High-Risk Patients With Chronic Obstructive Pulmonary Disease: The ASCENT-COPD Randomized Clinical Trial. *JAMA*. 2019;321(17):1693–1701, eTable 6.

Figure captions

Figure. 1.

Adjudication flow chart for (a) adverse events and (b) deaths ~~(c) SUMMIT secondary endpoint~~.

~~CED, common end date for participants; CV, cardiovascular; MI, myocardial infarction; TIA, transient ischaemic attacks; UA, unstable angina.~~

The 450 events in (a) refer to the four main components of the predefined major adverse cardiovascular events (MACE): fatal or non-fatal myocardial infarction, fatal or non-fatal stroke, unstable angina (all non-fatal) and transient ischaemic attack (all non-fatal).

*Sites entered adverse events using the usual process of describing the event with a "verbatim term". The verbatim term was coded by a central automatic coding procedure to a Medical Dictionary for Regulatory Activities preferred term. If this Medical Dictionary for Regulatory Activities preferred term matched a pre-specified list (see Online Supplementary Appendix B, Figure S1 and Table S1) then this triggered the adjudication process.

~~Round 1 = Independent review by three committee members; Round 2 = Consensus discussion among all committee members.~~

~~*SUMMIT secondary endpoint was time to first on-treatment CV composite event (which includes on-treatment CV death). Patients may have experienced multiple CV events, but only the first was used in the analysis; ‡Total = fatal + non-fatal~~

Commented [JL8]: *Moved to become Table 2 to address Reviewer 2, comments 1 and 5.*

Commented [JL9]: *Authors, these acronyms have been removed from the figure in line with the Editor's comment, however 'PR death' has not been amended. Please do advise if there is a suitable term that can be used in place of this abbreviation.*

Commented [JL10]: *Added to address Reviewer 2, comment 3.*

Commented [JL11]: *Added to address Reviewer 2, comment 2.*

Table 1

Agreement (diagonal) of cause of death between Primary Investigator and Clinical Endpoint Committee. Percentages on diagonal show agreement by clinical endpoint committee of primary investigator cause.

	Primary Investigator CAUSE OF DEATH					
Clinical Endpoint Committee ADJUDICATED CAUSE OF DEATH	Cardiovascular	Pulmonary	Cancer	Other	Unknown	Total ~~(%)~~
Cardiovascular	256 (72%)	24	0	74	105	459 (43%)
Pulmonary	21	73 (62%)	0	33	11	138 (13%)
Cancer	9	8	192 (99%)	23	11	243 (23%)
Other	19	3	0	61 (28%)	6	89 (8%)
Unknown	52	10	2	27	41 (24%)	132 (12%)
Total	357 (34%)	118 (11%)	194 (18%)	218 (21%)	174 (16%)	1061

Commented [JL12]: *Amended to address Reviewer 2, comment 7.*

Table 2

Commented [JL13]: *Moved from Figure 1 to address Reviewer 2, comments 1 and 5.*

Adjudicated First Cardiovascular Composite Events (Secondary Endpoint)*

Myocardial infarction	173 (25%)
Stroke	127 (18%)
Unstable Angina	83 (12%)
Transient ischaemic attack	34 (5%)
Procedural Death	2 (<1%)
Sudden Death	240 (35%)
Other cardiovascular Death	29 (4%)
Total	688

*SUMMIT secondary endpoint was time to first on-treatment cardiovascular composite event (which includes on-treatment cardiovascular death). Patients may have experienced multiple cardiovascular events, but only the first was used in the analysis

Supplementary Material

Adjudication of cardiovascular events in patients with chronic obstructive pulmonary disease: SUMMIT trial

Supplementary Appendix A

Principles of Operation of the SUMMIT Clinical Endpoint Committee (CEC) Version 003

This document should be used in conjunction with the Charter developed for the SUMMIT CEC (**HZC113782)** protocol and will be updated at subsequent meetings.

Version 001 dated 15Apr2012
Version 002 dated 02Aug2012
Version 003 dated 29Jun2014

Assignment of cause of death

The Clinical Endpoint Committee will designate cause of death by probable cause. Causes of death will be grouped by general categories, e.g. pulmonary, cardiovascular, cancer, or other. If a cause of death cannot be ascertained, the cause of death will be classified as unknown. The general principles and methods used in this classification are listed:

Source documentation will be obtained to help in the assignment of cause of death see Appendix 1 and the form issued in Appendix 4.

The ~~eCRF~~ electronic case report form within the electronic Virtual Clinical Adjudication System (~~VCAS;~~ PAREXEL Inc, Waltham, MA) ~~VCAS system~~ is shown in Appendix 2.

If medical records are inadequate and cannot be obtained as affirmatively stated in the documentation, a cause of death will be adjudicated based on the best available evidence of record. When information is incomplete, the adjudication of cause of death may rely on information derived from the participant's relatives or the site physician. The use of this information will inform assignment of cause of death based on consistency of the information as well as the specificity of the information. For example, the attribution of death from a particular type of cancer may be quite specific for the purposes of this study. However, terms such as 'heart attack' may be considered inconclusive with respect to this study in which cardiovascular adverse events are a major outcome.

Medical diagnoses will be based on the principle of Reasonable Degree of Medical Certainty, which can be defined as follows:

- The diagnosis is more likely than not
- The diagnosis is based on the same degree of certainty that would be used in the daily practice of medicine
- A majority of experts in the field would agree with the diagnosis.

The primary cause of death should be attributed to the disorder that causes the patient to present for medical treatment. This should be distinguished from terminal events that are the immediate cause of death.

- For example, if a patient is admitted to the hospital with a COPD exacerbation, from which they do not fully recover, and the patient subsequently develops complications such as pneumonia, respiratory failure, renal failure, sepsis or myocardial infarction, the

primary cause of death will be attributed to COPD. The myocardial infarction will be classified as a cardiovascular event (e.g. myocardial infarction, type 2).

- For example, if a patient undergoes surgery for cancer and dies from complications of the surgery or during the immediate postoperative period, the primary cause of death will be attributed to cancer, even if the cancer was potentially curable by the surgery.

- For example in general, if a patient is admitted to the hospital with pneumonia and develops complications such as respiratory failure, gastrointestinal bleeding, etc. the cause of death will be attributed to pneumonia. If it is unclear if a patient is admitted with a COPD exacerbation or pneumonia, the cause of death will be based on the hospital admission chest radiograph. If pneumonia is present on the admitting chest radiograph, the cause of death will be designated pneumonia. If pneumonia is present only on subsequent chest radiographs, the cause of death will be designated as COPD.

1. Cause of death

Cardiovascular death

Sudden death

Sudden death is a term generally denoting a presumed arrhythmic death when the death is witnessed and another cause cannot be identified. However, it is more likely that the cause is cardiac in nature if the death (not necessarily witnessed) occurred within a reasonable time frame (i.e. <1 hour) of the patient last being seen alive and without evidence of clinical deterioration. If the interval between death and last being observed alive is between 1 and 24 hours and there is no observation of a significantly deteriorating medical condition, then the death is less certain to be of cardiac origin and will be classified as unwitnessed sudden death. If the last observation of the deceased is >24 hours, and there is no other known cause of death, there is less certainty that the cause of death is cardiovascular and will be classified as unknown.

Sub-categories of sudden death are as follows:

Witnessed (observed in usual health within 1 hour of death event)
Unwitnessed (observed in usual health between 1–24 hours of death event)

In cases of out of hospital death, the site coordinator or site physician should interview family or witnesses to ascertain the following information: see Appendix 5 for the actual form.

- When was the person last known to be alive?
- When was the person found to be deceased?
- What were the events surrounding the death?
- Did the deceased have any symptoms or change in health status that preceded the death? Special reference should be made to shortness of breath, fever, infection, chest pain, abdominal pain, fainting, seizures, paralysis and change in mental status.
- Were there recent medical visits or recent changes in medication?
- Was an autopsy performed?

Myocardial infarction

Thygesen 2007

In general, the diagnosis of myocardial infarction will require pathologic evidence, or evidence of medical record including electrocardiographic tracings, blood enzyme measurements, and compatible clinical findings.

Criteria for acute myocardial infarction

The term myocardial infarction should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischaemia. Under these conditions any one of the following criteria meets the diagnosis for myocardial infarction:

- Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischaemia with at least one of the following:
  - Symptoms of ischaemia;
  - ECG changes indicative of new ischaemia [new ST-T changes or new left bundle branch block (LBBB)];
  - Development of pathological Q waves in the ECG;
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
- Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischaemia, and accompanied by presumably new ST elevation, or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.
- For percutaneous coronary interventions (PCI) in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL are indicative of peri-procedural myocardial necrosis. By convention, increases of biomarkers greater than 3 × 99th percentile URL have been designated as defining PCI-related myocardial infarction. A subtype related to a documented stent thrombosis is recognized.
- For coronary artery bypass grafting (CABG) in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL are indicative of peri-procedural myocardial necrosis. By convention, increases of biomarkers greater than 5 × 99th percentile URL plus either new pathological Q waves or new LBBB, or angiographically documented new graft or native coronary artery occlusion, or imaging evidence of new loss of viable myocardium have been designated as defining CABG-related myocardial infarction.
- Pathological findings of an acute myocardial infarction.

Criteria for prior myocardial infarction

Any one of the following criteria meets the diagnosis for prior myocardial infarction:

- Development of new pathological Q waves with or without symptoms.
- Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischaemic cause.
- Pathological findings of a healed or healing myocardial infarction.

In circumstances where the source documents such as electrocardiogram tracings or enzyme levels are not available, the committee may base a diagnosis of myocardial infarction on other reliable medical sources, but should not ordinarily accept death certificate or witness statements for this diagnosis.

Stroke

In general, the diagnosis will require compatible clinical findings. With respect to diagnosis of stroke: Although brain imaging is ordinarily required for the diagnosis of stroke, if the clinical syndrome is compelling (e.g. hemiparesis and aphasia) and follows a typical clinical course for stroke, this may be adequate to adjudicate the case as a stroke. Classification of the type of stroke will usually require either supportive imaging or pathological evidence. In some cases, a haemorrhagic stroke may be supported by a compatible clinical syndrome associated with supportive cerebrospinal fluid examination.

Definition of stroke types:

a) ISCHAEMIC: Infarction of brain tissue as a result of either occlusion of a brain artery by any mechanism (e.g. thrombosis, embolism), or decreased perfusion selectively affecting specific brain arterial territories (e.g. borderzone infarction).

b) HAEMORRHAGIC: Damage directly resulting from sudden extravasation of blood into the brain tissue (i.e. intracerebral) or the spaces surrounding the brain (e.g. subarachnoid).
c) INDETERMINATE: Information is insufficient to classify.

When a stroke leads to a chronic disabling condition that results in death, the cause of death will be adjudicated as stroke.

Procedural death

A subject with ~~CV~~ cardiovascular disease is taken into hospital for an operation related to cardiovascular disease (e.g. percutaneous coronary intervention ~~(PCI)~~, coronary artery bypass graft ~~(CABG)~~ or during insertion of other cardiac device).

Pulmonary death

COPD without pneumonia

For the purpose of adjudication, an episode of pneumonia that occurs >5 days after onset of the terminal illness will be adjudicated as COPD without pneumonia. The intent is to exclude episodes of pneumonia that are secondary complications of a COPD exacerbation, such as ventilator- or healthcare-associated pneumonias.

COPD with pneumonia

For the purpose of this study, pneumonia is generally defined as a clinical syndrome compatible with pneumonia supported by radiographic evidence. It would be uncommon for a person with COPD to have pneumonia without symptoms compatible with a COPD exacerbation; however, it is conceivable that such an event might occur. In that case, the death will be coded as 'Pulmonary – other', with the cause specified as pneumonia.

Pulmonary embolism

For the purpose of adjudication, this diagnosis should be supported by a compatible clinical syndrome supported by imaging or pathological evidence. In the absence of definitive imaging or pathological evidence, this diagnosis should be supported by a high clinical likelihood supported by laboratory and clinical evidence (e.g. evidence of venous thrombosis) as well as a clinical diagnosis of the treating physicians.

Other respiratory deaths

If the death is not related to any of the other respiratory categories although is pulmonary in nature it will be classified as other respiratory death, e.g. pneumothorax, acute upper airway obstruction, pulmonary haemorrhage, or pneumonia in the absence of a COPD exacerbation that are not otherwise specified.

Cancer

All diagnoses of cancer should generally be corroborated by the primary medical record. This should include imaging studies, histologic diagnoses, operative or procedure notes, and records of treatment. If the primary medical record cannot be obtained to confirm the diagnosis, this should be

affirmatively stated in the documentation, and the committee will determine a diagnosis based on their best judgment. Haematological malignancies will be classified as cancer for the purpose of adjudication.

Patients who die with an uncured cancer that would be expected to be fatal will be designated as dying from the cancer. Exceptions to this may include cancers that if left untreated would not be expected to lead to death within 5 years. Examples of such cancers include non-melanoma skin cancers, localised prostate cancer or low-grade haematological malignancies.

For example, a patient with documented gastric cancer who dies of gastrointestinal haemorrhage will be classified to have died from gastric cancer. A patient who dies from neutropenic sepsis while undergoing chemotherapy for lymphoma will be classified as dying from lymphoma.

Sub-categorisation of cancer death will be lung, breast, colorectal or other. Other cancers will be submitted as free text.

Death other specify

If a subject commits suicide (e.g. by shooting themselves in the head, taking an overdose of pills, jumping off a bridge and drowning) the cause of death will be designated as 'Other – suicide', not 'Other (mode of suicide)'.

If a subject has an accident and causes injury to their head that causes death, it should be classified as other and specified as traumatic brain injury (not head trauma, brain trauma, etc.)

Death unknown

In some circumstances, the cause of death cannot be determined based on the evidence available to the committee. This includes deceased who are found deceased after >24 hours have elapsed since they were last observed in their usual state of health and where no other cause of death is apparent. The cause of death may be unknown either, because the medical information is adequate but the cause of death is 'indeterminate'. Such cases should be sub-categorised as indeterminate. In some cases, medical information may exist, but is not available for review. In those cases, the case should be sub-categorised as 'inadequate information'.

Procedure for dealing with multiple ~~SAEs~~ serious adverse events for a single death

If a subject has multiple fatal serious adverse events~~SAEs~~, these will be combined into one death episode in virtual clinical adjudication system ~~VCAS~~ and adjudicated as one death event.

2. Determination of COPD relatedness

All cases will have a secondary classification to determine whether the death is related to COPD. The possible choices are NO/UNLIKELY, YES/PROBABLE, UNKNOWN.

1. All cases where primary cause of death is COPD will be classified as YES.

2. In cases where primary cause of death is NOT COPD the classification of COPD relatedness will be based on the sequence of terminal events:

- If the terminal event is documented to be hypercapnic respiratory failure or failure to wean from a ventilator the case will be classified YES.
  - For example, patient dies in hospital on ventilator, but succumbs to fatal pneumonia, arrhythmia, or care is withdrawn.
- If the patient would have been judged to have survived the terminal illness had COPD not been present, the case will be classified YES
  - For example, patient dies from Stage I lung cancer because they have insufficient lung function to undergo surgery.
  - For example, patient has pneumonia or influenza that is fatal.
- If the death occurs at home, where the patient is receiving palliative care for advanced COPD, the case will be classified YES.
  - For example, a patient receiving continuous oxygen, confined to bed and chair, with cor pulmonale, or with advanced malnutrition.
- If the terminal event is NOT respiratory, and would be likely fatal for patients without COPD, the case will be classified NO.
  - For example, death from metastatic cancer, cerebral haemorrhage, severe cardiomyopathy or cardiogenic shock.
- If there is another clear explanation for terminal respiratory failure that would likely have occurred in patients without COPD, then the case will be classified NO.
  - For example respiratory failure secondary to ~~CV~~cardiovascular~~a~~, drug overdose or asphyxia.

3. If the data are inadequate to make a clear YES/PROBABLE or NO/UNLIKELY classification, it will be designated as UNKNOWN, based on the best evidence available. UNKNOWN will be classified as either, indeterminate or inadequate information.

Cardiovascular events

For the purpose of this study, the cardiovascular endpoint comprises ~~MI~~myocardial infarction, stroke, ~~TIA~~transient ischaemic attack, unstable angina and on-treatment cardiovascular death. The cardiovascular electronic case report form~~CRF~~ page is shown in Appendix 3. The committee will require supportive evidence from the medical records in order to classify an adverse event as a cardiovascular event for this study.

Non-serious possible cardiovascular adverse event only: Investigator declaration, Appendix 6

Non-serious cardiovascular adverse events occasionally are being reported with no source documentation available. This is usually caused by subject self-reporting/diary entry at scheduled study visit, thus there is no evidence for protocol-defined event.

The non-serious possible cardiovascular adverse event only: Investigator Declaration, Appendix 6, was developed to find out if the site investigator believed the reported event could be a study endpoint (unstable angina, myocardial infarction, transient ischaemic attack or stroke) by answering yes or no to question #1. If yes, further documentation is requested of the site. If no, the site investigator will be asked to sign, date and return the form to PAREXEL.

Chest pain

In cases where a Non-Serious ~~AE~~adverse event~~-~~ of chest pain or a similar term triggers an event and the clinical study site is unable to obtain medical evidence, the site investigator

will be asked to answer question #2 within 'The non-serious possible cardiovascular adverse event only: Investigator declaration' to assess cardiac cause.

If the site investigator declares that the event is '**non-cardiac**' chest pain, and there is no medical evidence to review, then the event will be administratively determined (deleted in virtual clinical adjudication system~~VCAS~~) not to be a protocol defined endpoint and will not go to the committee for further review. If there is medical evidence of record for the committee to review such as clinical notes, ~~SAE~~ serious adverse event reports, laboratory findings, or ~~ECGs~~electrocardiographs, then the event will be reviewed by the committee regardless of the investigator's declaration.

Triage process for ~~AEs~~ adverse events

It was agreed by the CEC and ~~GSK~~ GlaxoSmithKline plc. to create a triage process for ~~AEs~~ adverse events only (note: all ~~SAEs~~ serious adverse events automatically go to the independent round). This triage process in virtual clinical adjudication ~~VCAS~~ would initially be completed by one CEC member only. The ~~eCRF~~ electronic case report form in ~~VCAS~~ asks 'This is an event which needs further adjudication as it may be ~~TIA~~transient ischaemic attack, stroke, ~~UA~~unstable angina or myocardial infarction~~MI~~' [Yes/No], If 'Yes' it would go to the 'independent' round for full committee review or if 'No' the event is considered complete.

Myocardial infarction

Generally, the definition provided by Thygesen 2007 will be used to determine myocardial infarction.

'The diagnosis of myocardial infarction will require pathologic evidence, or evidence of medical record including electrocardiographic tracings, blood enzyme measurements, and compatible clinical findings'.

Myocardial infarctions will be sub-classified as follows:

- Type 1 – Spontaneous myocardial infarction related to ischaemia due to a primary event such as plaque erosion or rupture fissuring or dissection.
- Type 2 – Myocardial infarction secondary to ischaemia due to imbalance between oxygen demand and supply, e.g. coronary spasm, anaemia or hypotension. This type of event would typically occur in the context of another illness that may or may not be fatal.
- Procedure related – Myocardial infarction associated with percutaneous coronary intervention ~~PCI~~ or in association with a coronary artery bypass graft~~CABG~~. This category includes both type 4 and type 5 myocardial infarction according to the Universal definitions.

(Type 3 myocardial infarctions are associated with sudden death and will be coded as a death event under either sudden death or myocardial infarction.)

Unstable angina

Symptoms of myocardial ischaemia at rest (chest pain or equivalent) or an accelerating pattern of angina with frequent episodes associated with progressively decreased exercise capacity that prompts an unscheduled visit to a healthcare facility. One of the following should also be observed in the absence of evidence of acute myocardial infarction:

1) New or worsening ST or T-wave changes on resting ~~ECG~~ electrocardiograph

   a. ST elevation

      New ST elevation at the J point in two anatomically contiguous leads with the cut-off points: ≥0.2 mV in men (>0.25 mV in men <40 years) or ≥0.15 mV in women in leads V2–V3 and/or ≥0.1 mV in other leads.

   b. ST depression and T-wave changes
      New horizontal or down-sloping ST depression ≥ 0.05 mV in two contiguous leads; and/or new T inversion ≥0.1 mV in two contiguous leads.

      It is recognised that lesser ~~ECG~~ echocardiograph abnormalities may represent an ischaemic response and may be accepted under the category of abnormal ~~ECG~~ echocardiograph findings.

2) Definite evidence of myocardial ischaemia on myocardial scintigraphy (clear reversible perfusion defect), stress echocardiography (reversible wall motion abnormality), or MRI (myocardial perfusion deficit under pharmacologic stress) that is believed to be responsible for the myocardial ischaemic symptoms/signs

3) Angiographic evidence of ≥70% lesion and/or thrombus in an epicardial coronary artery that is believed to be responsible for the myocardial ischaemic symptoms/signs.

4) Need for coronary revascularisation procedure (percutaneous coronary intervention ~~PCI~~ or coronary artery bypass graft~~CABG~~).

Stroke

In general, the diagnosis will require compatible clinical findings. Classification of the type of stroke will usually require either supportive imaging or pathological evidence. In some cases, a haemorrhagic stroke may be supported by a compatible clinical syndrome associated with supportive cerebrospinal fluid examination.

Definition of stroke types:

a) ISCHAEMIC: Infarction of brain tissue as a result of either occlusion of a brain artery by any mechanism (e.g. thrombosis, embolism), or decreased perfusion selectively affecting specific brain arterial territories (e.g. borderzone infarction).
b) HAEMORRHAGIC: Damage directly resulting from sudden extravasation of blood into the brain tissue (i.e. intracerebral) or the spaces surrounding the brain (e.g. subarachnoid).
c) INDETERMINATE: Information is insufficient to classify, but the clinical course is suggestive of a stroke.

Transient ischaemic attack

Temporary focal neurologic deficit is defined as either witnessed by a physician or recorded by a physician as a credible and objectively witnessed event, AND presumably resulting from brain ischaemia, AND lasting less than 24 hours, AND without any evidence of appropriate ischaemic

Commented [JL1]: *Authors, acronyms have been removed from this file in line with the Editor's comment, however 'ST' and 'T wave' have not been amended. Please do advise if there are suitable terms that can be used in place of these abbreviations.*

changes in either ~~CT~~ computed tomography or ~~MRI~~ magnetic resonance imaging if either of these obtained.

None of the above

The event does not meet the definition of an adverse cardiovascular event as listed above.

Related to previous ~~CV~~ cardiovascular event

If based on the information in the endpoint adjudication package, the CEC determines this is related to a previously adjudicated event then it will be marked as such and not counted as a new event. The previous ~~AE~~adverse event reference ~~ID~~ identifier will be added to the ~~eCRF~~ electronic case report form by the CEC.

Appendix 1

Documents provided to the Clinical Endpoint Committee (CEC) for adjudication

Whenever possible, potential endpoints will be sent to the CEC only when all appropriate case report forms ~~(CRFs)~~ and a completed dossier of the information have been obtained. Also, if multiple related or evolving events occur in a single subject, whenever possible, the set of the events will be kept together and sent to the CEC only when all documents for all events are complete. These may include but are not limited to:

- Death certificate
- Discharge summary
- Imaging and procedure notes
- Surgical operation reports
- Hospital records and outpatient records
- Physician notes (i.e. from office or clinic)
- Witness accounts, including non-hospital death where narratives from friends and relatives. A proforma will be developed with questions
- Autopsy reports
- Pathology reports
- Serious ~~AE~~adverse event reports
- ~~ECG~~ Echocardiograph reports
- Pertinent radiologic reports (i.e. plain films/~~MRI~~magnetic resonance imaging/~~CT~~computed tomography)
- ~~CRF~~ Case report form reports, including con-meds, past history, demography
- Labs including troponins and cardiac enzymes
- Coronary angiogram reports (with no intervention)
- Carotid ultrasound reports
- Angiogram of head and neck procedures coronary artery bypass graft~~CABG~~, and percutaneous coronary interventions ~~PCIs~~ reports
- Head computed tomography ~~CT~~ scans and magnetic resonance images~~MRIs~~
- Other

Appendix 2

Tier	Questions	Responses
1	Classify the primary cause of death	☐ **Cardiovascular** ☐ Sudden Death* ☐ Witnessed less than 1 hour ☐ Unwitnessed 1–24 hours ☐ Myocardial Infarction ☐ Stroke ☐ Hemorrhagic ☐ Ischemic ☐ Indeterminate ☐ Procedural death (related to PCI, CABG or during insertion of other cardiac device) ☐ Other, specify _____ ☐ **Pulmonary** ☐ COPD ☐ with pneumonia ☐ without pneumonia ☐ Pulmonary embolism ☐ Other, specify _____ ☐ **Cancer** ☐ Lung ☐ Breast ☐ Colorectal ☐ Other, specify _____ ☐ **Other, specify** _____ ☐ **Unknown, specify (includes sudden death >24hrs)** ☐ inadequate information ☐ indeterminate
2	Was the death COPD related	☐ No or unlikely ☐ Yes or probable ☐ Unknown ☐ inadequate information ☐ indeterminate
Comments (Remark on adjudication rationale):		
* defined as per MERIT -HF trial , Lancet 1999		

Abbreviations: CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; MERIT-HF, Metoprolol CR/XL Randomised Intervention Trial in-Congestive Heart Failure; PCI, percutaneous coronary intervention.

Appendix 3

Tier	Questions	Responses
1	Is this event a	☐ Myocardial Infarction ☐ Type 1 ☐ Type 2 ☐ Procedural related ☐ Unstable Angina ☐ Stroke ☐ Hemorrhagic ☐ Ischemic ☐ Indeterminate ☐ Transient Ischemic Attack ☐ None of the above A. ☐ No evidence for protocol defined CV event B. ☐ Related to previous CV event Adverse Event ID_____ _____
Comments (Remark on adjudication rationale):		

Abbreviation: CV, cardiovascular

Appendix 4

CEC Collection Form

Date			
Centre Number		**Subject Number**	
Clinical Event Term (AE term as entered in DataLabs)			
Event Onset Date			

Please provide the following source documents and make sure the centre/subject study numbers are marked on each document. Remove all patient identifiers. Check one box per line item and provide this form with the source returned:

	Source Document	Enclosed	Requested from facility	Updated in DataLabs	Not Available	Not Applicable
1	Death certificate					
2	Discharge summary					
3	Imaging and procedure notes					
4	Surgical operation reports					
5	Hospital records and outpatient records					
6	Physician notes (from office or clinic)					
7	**Non-hospital death witness account with details from friends and relatives (non-hospital death questionnaire, Appendix 5)					
8	Autopsy reports					
9	Pathology reports					
10	SAE reports (if not already submitted)					
11	ECG reports					
12	Pertinent radiologic reports					
13	CRF reports (please make sure con-meds, past history, demography are updated in DataLabs)					
14	Labs including troponins and cardiac enzymes					
15	Coronary angiogram reports (with no intervention)					
16	Carotid ultrasound reports					
17	Angiogram of head and neck procedures, CABG, PCI reports					
18	Others as requested					

Investigator's Signature: ..... **Date:** .....

- **Please return the completed table, including the Investigator's signature, with all available source documents to PAREXEL**
- **To assist with the CEC review, kindly respond within 2 weeks.**

Abbreviations: AE, adverse event; CABG, coronary artery bypass graft; CEC, Clinical Endpoint Committee; COPD, chronic obstructive pulmonary disease; CRF, case report form; ECG, echocardiograph; PCI, percutaneous coronary intervention; SAE, serious adverse event.

Appendix 5

GSK Protocol HZC113782 SUMMIT –

Non-hospital death witness questionnaire

Date			
Centre Number		**Subject Number**	
Event Onset Date			

**In cases of out of hospital death, the site coordinator or site physician should interview family or witnesses to ascertain the following information:

1	**When was the person last known to be alive?**	
2	**When was the person found to be deceased?**	
3	**What were the events surrounding the death?**	
4	**Did the deceased have any symptoms or change in health status before the death? Special attention should be made to shortness of breath, fever, infection, chest pain, abdominal pain, fainting, seizures, paralysis and change in mental status.**	
5	**Were there recent medical visits or recent changes in medication?**	
6	**Was an autopsy performed?**	

Investigator's Signature: ..... **Date**: .....

- **If applicable, please return the completed questionnaire, including the Investigator's signature, with CEC Collection Form and associated documents to PAREXEL**
- **To assist with the CEC review, kindly respond within 2 weeks.**

Abbreviation: CEC, Clinical Endpoint Committee.

Appendix 6

GSK Protocol HZC113782 SUMMIT

Non-serious possible cardiovascular adverse events only
Investigator declaration

Date			
Centre Number		**Subject Number**	
Clinical Event Term (AE term as entered in DataLabs)			
Event Onset Date			

If no source documents are available due to subject self-reporting for CV events, site investigator will need to complete this form:

****Please complete for chest pain or similar term regardless of your assessment of cause.**

1. Is this event part of a study endpoint (myocardial infarction, unstable angina, transient ischaemic attack or stroke)?
□ YES □NO

If YES, please provide additional evidence (documentation) to support this assessment.
If NO, please sign and date this form and return per instructions below.

2. If this event is CHEST PAIN or a similar term, then complete the following:

Please tick to indicate which one of the following applies:
___ This event is likely cardiac or ischaemic chest pain
____This event is NOT likely cardiac or ischaemic in origin
___ It is indeterminate whether this event is cardiac or ischaemic in origin

Investigator comments:

_____ _____

Investigator's Signature **Date**

- **If applicable, please return the completed questionnaire, including the Investigator's signature, with CEC Collection Form and associated documents to PAREXEL via fax: +1 781 434 5957 or email: GSKSUMMITCEC@PAREXEL.com**
- **To assist with the CEC review, kindly respond within 2 weeks.**

Abbreviations: AE, adverse event; CEC, Clinical Endpoint Committee; CV, cardiovascular.

Formatted: Font: 11 pt, Not Bold

Formatted: Font: 11 pt, Not Bold

Supplementary Appendix B

Figure S1.

Number of cardiovascular events triggered by ~~MedDRA~~Medical Dictionary for Regulatory Activities preferred term.

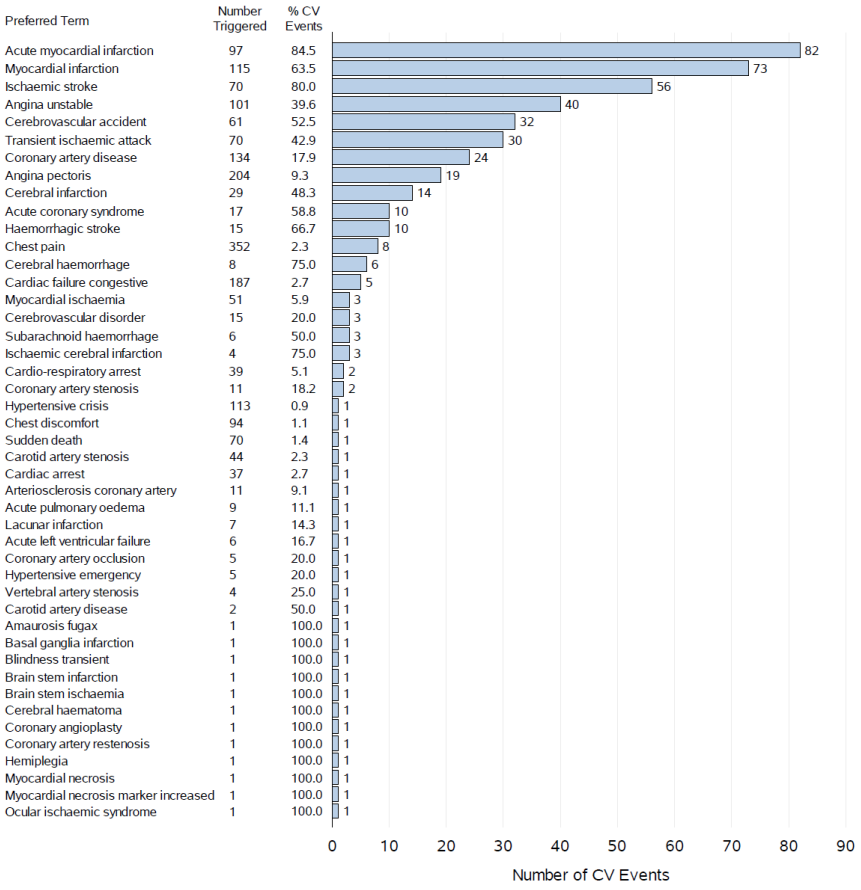


Table S1.

Triggered ~~MedDRA~~Medical Dictionary for Regulatory Activities preferred terms that resulted in no ~~CV~~cardiovascular events.

Preferred term	Number triggered	Number of ~~CV~~ cardiovascular events
Cardiac failure	160	0
Syncope	92	0
Peripheral arterial occlusive disease	91	0
Palpitations	74	0
Aortic aneurysm	54	0
Cardiac failure chronic	50	0
Hypoesthesia	50	0
Ventricular extrasystoles	34	0
Peripheral artery stenosis	24	0
Arteriosclerosis	21	0
Cor pulmonale	21	0
Presyncope	21	0
Cardiac failure acute	20	0
Peripheral ischaemia	20	0
Pulmonary congestion	20	0
Intermittent claudication	19	0
Peripheral venous disease	19	0
Pulmonary oedema	19	0
Vascular encephalopathy	18	0
Sudden cardiac death	17	0
Loss of consciousness	16	0
Ventricular tachycardia	16	0
Congestive cardiomyopathy	15	0
Ischaemic cardiomyopathy	14	0
Left ventricular failure	14	0
Cardiopulmonary failure	13	0
Femoral artery occlusion	13	0
Somnolence	13	0
Iliac artery occlusion	12	0
Carotid arteriosclerosis	10	0
Circulatory collapse	9	0
Confusional state	9	0
Left ventricular dysfunction	9	0
Left ventricular hypertrophy	9	0
Carotid artery occlusion	8	0
Cerebral arteriosclerosis	8	0
Lethargy	8	0
Pain in jaw	8	0
Seizure	8	0
Aortic aneurysm rupture	7	0
Ventricular fibrillation	7	0
Vertebrobasilar insufficiency	7	0

Preferred term	Number triggered	Number of ~~CV~~ cardiovascular events
Cerebral ischaemia	6	0
Diabetic microangiopathy	6	0
Diastolic dysfunction	6	0
Aphonia	5	0
Cardiovascular disorder	5	0
Cerebrovascular insufficiency	5	0
Epilepsy	5	0
Accelerated hypertension	4	0
Arterial occlusive disease	4	0
Blindness	4	0
Bradyarrhythmia	4	0
Brain oedema	4	0
Cardiogenic shock	4	0
Raynaud's phenomenon	4	0
Subclavian artery stenosis	4	0
Tachyarrhythmia	4	0
Aneurysm	3	0
Aortic dissection	3	0
Aphasia	3	0
Arterial stenosis	3	0
Cardiac fibrillation	3	0
Cardiomegaly	3	0
Cardiovascular insufficiency	3	0
Cerebral microangiopathy	3	0
Cyanosis	3	0
Dilatation atrial	3	0
Hypovolemic shock	3	0
Intracranial aneurysm	3	0
Right ventricular failure	3	0
Vascular graft occlusion	3	0
Venous occlusion	3	0
Ventricular arrhythmia	3	0
Ventricular hypokinesia	3	0
Arterial stent insertion	2	0
Atrial thrombosis	2	0
Cardiac discomfort	2	0
Carotid artery aneurysm	2	0
Carotid bruit	2	0
Catheterisation cardiac	2	0
Coma	2	0
Convulsions local	2	0
Coronary artery thrombosis	2	0
Coronary ostial stenosis	2	0
Diabetic vascular disorder	2	0
Dysarthria	2	0
Ejection fraction decreased	2	0
Hemiparesis	2	0
Hyporeflexia	2	0

Preferred term	Number triggered	Number of ~~CV~~ cardiovascular events
Intraventricular haemorrhage	2	0
Orthopnoea	2	0
Peripheral coldness	2	0
Poor peripheral circulation	2	0
Sensory loss	2	0
Speech disorder	2	0
Troponin increased	2	0
Vasoconstriction	2	0
Amaurosis	1	0
Apraxia	1	0
Arterial bruit	1	0
Arteriogram coronary	1	0
Basilar artery occlusion	1	0
Basilar artery thrombosis	1	0
Blindness unilateral	1	0
Brain natriuretic peptide increased	1	0
Brain stem stroke	1	0
Cardiac aneurysm	1	0
Cardiac death	1	0
Cardiac disorder	1	0
Cardiac function disturbance postoperative	1	0
Cardiac pacemaker evaluation	1	0
Cardiac pacemaker insertion	1	0
Cardiac ventricular thrombosis	1	0
Cardio-respiratory distress	1	0
Cerebral artery stenosis	1	0
Cerebral artery thrombosis	1	0
Complex partial seizures	1	0
Cor pulmonale acute	1	0
Cor pulmonale chronic	1	0
Coronary artery insufficiency	1	0
Coronary vascular graft occlusion	1	0
Diplegia	1	0
Disorientation	1	0
Dry gangrene	1	0
Extremity necrosis	1	0
Eye disorder	1	0
Generalised tonic-clonic seizure	1	0
Haemorrhage intracranial	1	0
Haemorrhagic cerebral infarction	1	0
Hypertensive cardiomyopathy	1	0
Intracranial pressure increased	1	0
Ischaemia	1	0
Motor dysfunction	1	0
Myocardial fibrosis	1	0
Neuritis cranial	1	0
Night blindness	1	0
Paresis	1	0

Preferred term	Number triggered	Number of ~~CV~~ cardiovascular events
Penetrating atherosclerotic ulcer	1	0
Pericarditis	1	0
Peripheral circulatory failure	1	0
Postictal paralysis	1	0
Pseudoangina	1	0
Pulseless electrical activity	1	0
Right atrial dilatation	1	0
Right atrial hypertrophy	1	0
Ruptured cerebral aneurysm	1	0
Seizure like phenomena	1	0
Shock haemorrhagic	1	0
Troponin I increased	1	0
Ultrasound Doppler abnormal	1	0
Vascular graft thrombosis	1	0
Vascular occlusion	1	0
Vascular pseudoaneurysm	1	0
Vascular stenosis	1	0
Ventricle rupture	1	0
Ventricular failure	1	0
Ventricular hypertrophy	1	0
Visual field defect	1	0

Table S2.

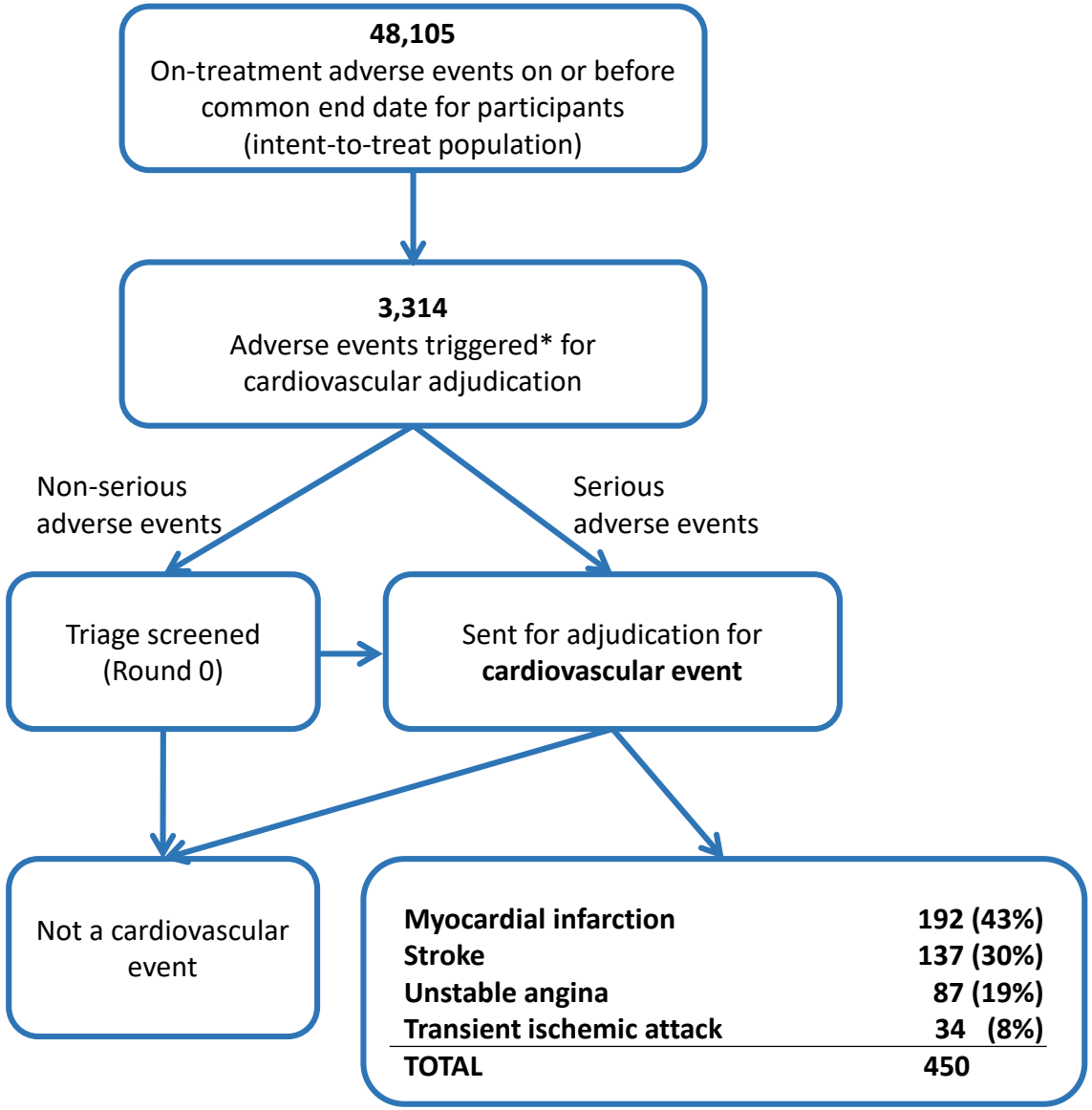
Agreement of individual adjudicators on round 1 with final committee adjudication of primary classification of death (~~cardiovascular~~cardiovascular, pulmonary, cancer, other cause or unknown).

	# cases reviewed	# agree with final adjudication	Percent agreement (%)
Adjudicator 1	800	648	81
Adjudicator 2	710	644	91
Adjudicator 3	653	551	84
Adjudicator 4	248	185	75
Adjudicator 5	753	652	87
Adjudicator 6	714	606	85
Total*	3,878	3,286	85

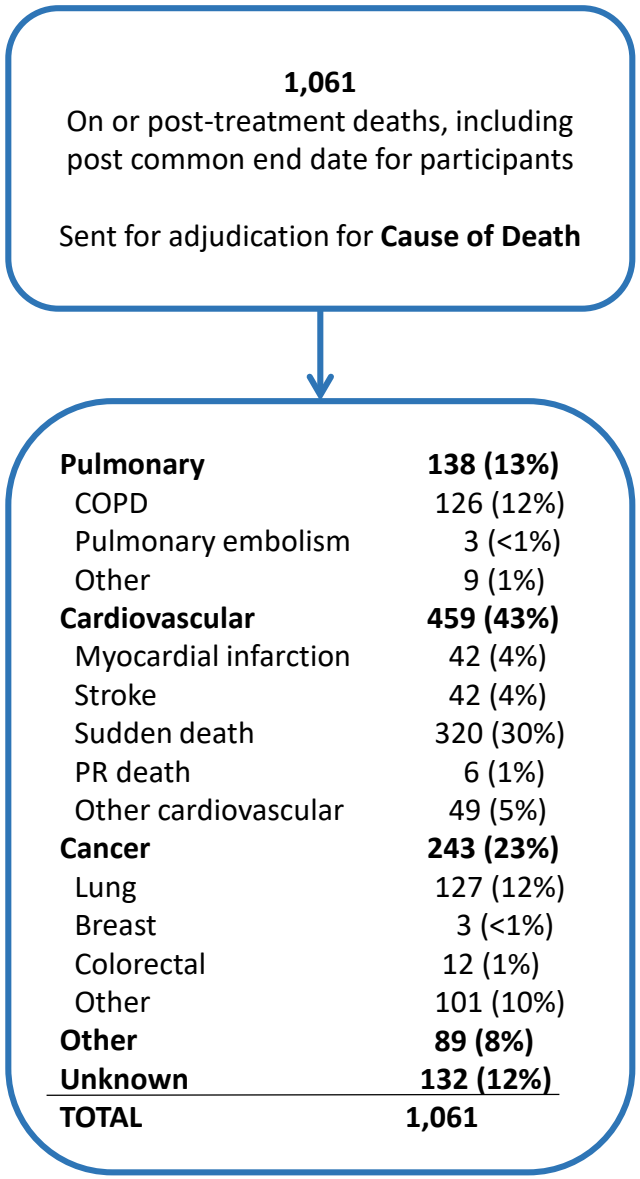
* There were more cases (3,878) than adverse events (3,314) because some adverse events were reviewed by more than one adjudicator in round 1.

Commented [JL2]: *Added to address reviewer 2, comment 6.*

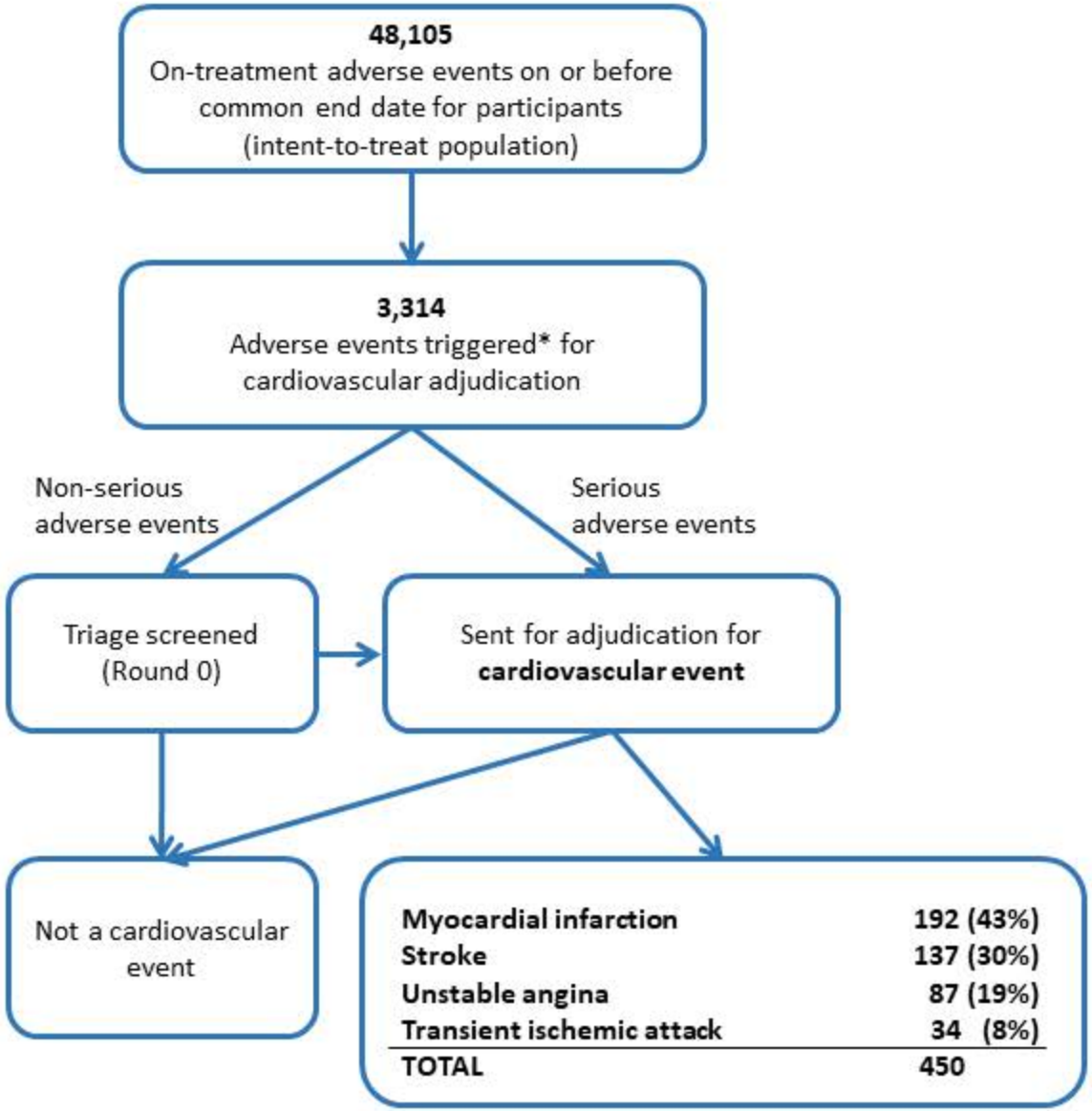
A


48,105
On-treatment adverse events on or before common end date for participants (intent-to-treat population)
3,314
Adverse events triggered* for cardiovascular adjudication
Non-serious adverse events
Serious adverse events
Triage screened (Round 0)
Sent for adjudication for cardiovascular event
Not a cardiovascular event
Myocardial infarction 192 (43%)
Stroke 137 (30%)
Unstable angina 87 (19%)
Transient ischemic attack 34 (8%)
TOTAL 450

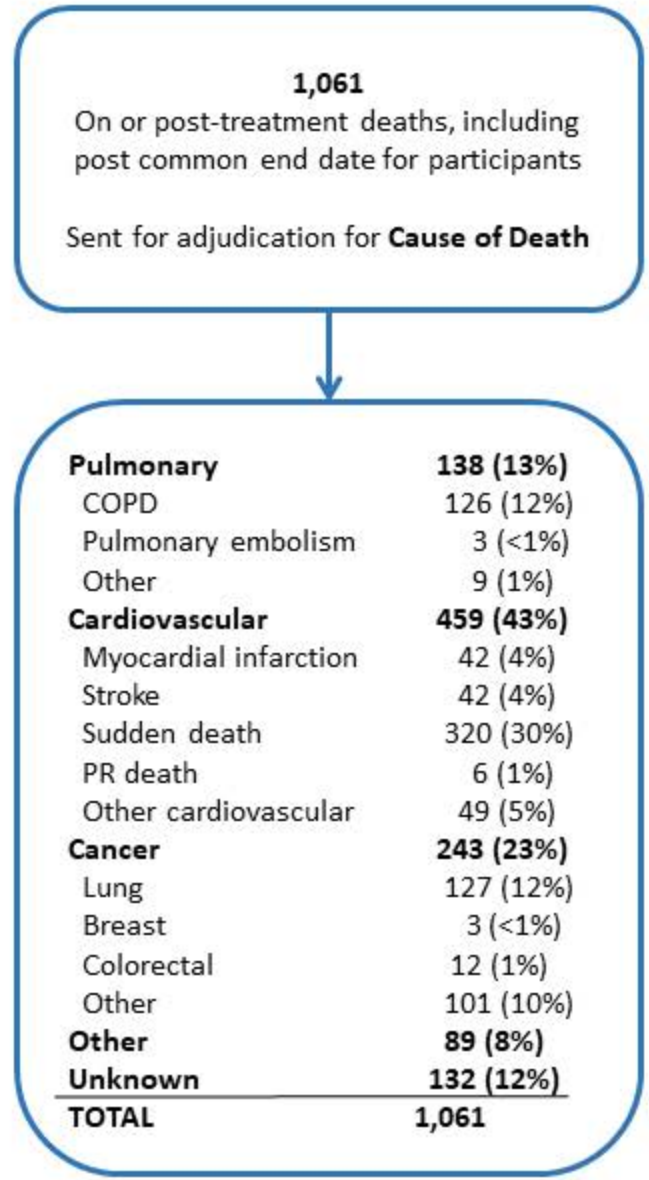
B


1,061
On or post-treatment deaths, including post common end date for participants
Sent for adjudication for Cause of Death
Pulmonary 138 (13%)
COPD 126 (12%)
Pulmonary embolism 3 (<1%)
Other 9 (1%)
Cardiovascular 459 (43%)
Myocardial infarction 42 (4%)
Stroke 42 (4%)
Sudden death 320 (30%)
PR death 6 (1%)
Other cardiovascular 49 (5%)
Cancer 243 (23%)
Lung 127 (12%)
Breast 3 (<1%)
Colorectal 12 (1%)
Other 101 (10%)
Other 89 (8%)
Unknown 132 (12%)
TOTAL 1,061

A


48,105
On-treatment adverse events on or before common end date for participants (intent-to-treat population)
3,314
Adverse events triggered* for cardiovascular adjudication
Non-serious adverse events
Serious adverse events
Triage screened (Round 0)
Sent for adjudication for cardiovascular event
Not a cardiovascular event
Myocardial infarction 192 (43%)
Stroke 137 (30%)
Unstable angina 87 (19%)
Transient ischemic attack 34 (8%)
TOTAL 450

B


1,061
On or post-treatment deaths, including post common end date for participants
Sent for adjudication for Cause of Death
Pulmonary 138 (13%)
COPD 126 (12%)
Pulmonary embolism 3 (<1%)
Other 9 (1%)
Cardiovascular 459 (43%)
Myocardial infarction 42 (4%)
Stroke 42 (4%)
Sudden death 320 (30%)
PR death 6 (1%)
Other cardiovascular 49 (5%)
Cancer 243 (23%)
Lung 127 (12%)
Breast 3 (<1%)
Colorectal 12 (1%)
Other 101 (10%)
Other 89 (8%)
Unknown 132 (12%)
TOTAL 1,061